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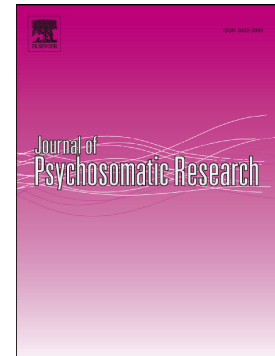
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Anxiety, depression and probability of live birth in a cohort of women with self-reported infertility in the HUNT 2 Study and Medical Birth Registry of Norway

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ABSTRACT

Objective: The ‘psychogenic’ hypothesis has a long history in the field of infertility. The present study investigated whether anxiety or depressive symptoms are associated with probability of subsequent live birth in a cohort of infertile women from the general population.

Methods: Using linked data from 12 987 women in the North-Trøndelag Health Study 1995-97 (HUNT 2) and the Medical Birth Registry of Norway (MBRN) a cohort of 467 women with self-reported infertility was followed prospectively in the MBRN for 11 years with regard to live birth. Anxiety and depressive symptoms were measured at baseline in HUNT 2 by the Hospital Anxiety and Depression Scale (HADS), i.e. the Anxiety (HADS-A) and Depression (HADS-D) sub-scales. The relationship between anxiety or depressive symptoms and live birth in the MBRN was analysed using Cox proportional hazards regression analysis.

Results: Anxiety and depressive symptoms were not associated with live birth rates. For anxiety symptoms, the crude hazard ratios (HR) for live birth was 1.004 (95% confidence interval (CI)=0.96; 1.05); adjusted HR=0.99 (95% CI=0.94; 1.04), for depressive symptoms crude HR was 0.98 (95% CI=0.92; 1.04); adjusted HR=1.01 (95% CI=0.94; 1.08). Among the 104 women with HADS-A \geq 8 and/or HADS-D \geq 8, 34 (32.7%) were registered with live birth in MBRN during the period of observation. However, 100 (27.6%) of the 363 women with both HADS-A \leq 7 and HADS-D \leq 7 were registered with live birth.

Conclusion: Anxiety and depressive symptoms are not associated with probability of live birth in women with self-reported infertility in the general population.

1. Introduction

The 'psychogenic hypothesis' has a long history in the field of infertility [1, 2] and women who struggle to get pregnant and their doctors may worry that mental distress may compromise their chance of pregnancy. The hypothesis that mental distress such as anxiety or depression cause or maintain infertility has been supported by several types of studies [3, 4], but no population-based studies have investigated the prospective association of mental distress with birth rates in infertile women. Lynch et al. (2014) recently showed that higher levels of a stress biomarker were associated with longer time-to-pregnancy and increased risk of infertility in presumably fertile women trying to get pregnant [5]. Other reports have been equivocal with regard to the hypothesised association between mental distress and fecundity in presumably fertile women [6, 7]. Notably, many studies of women who have sought help for their problems with getting pregnant (i. e. clinical studies) have concluded that depressive [8, 9] or anxiety symptoms [10] predict outcomes in artificial reproductive technology (ART) [8, 10-14]. However, these findings were contradicted by a meta-analysis by Boivin et al. (2011), which concluded that pre-treatment anxiety and depression do not predict pregnancy in ART [15]. Their findings, along with a recent meta-analysis by Frederiksen et al. (2015) [16], suggested the presence of a publication bias in favour of studies detecting positive associations between pre-treatment anxiety and depression, and pregnancy in ART.

To the best of our knowledge, there have been no investigations prospectively examining whether anxiety and depressive symptoms are associated with lower probability of subsequent live birth in infertile women who have not been included in a clinical study on the basis of ART-treatment. The aim of the present longitudinal study was therefore to investigate whether anxiety or depressive symptoms are associated with subsequent live birth rates in infertile women recruited from the general population. As clinic-based reports of prospective associations between anxiety or depression and fertility outcomes may be biased at inclusion

because women who suffer from mental distress are more likely to seek treatment than women who do not suffer from such distress [1, 2], and as help-seeking women may be older, with longer duration of infertility and higher prevalence of co-morbid somatic conditions than women who have not sought help [4, 17], we investigated the question if anxiety or depression are associated with live birth rates in infertile women in a population –based sample. We wanted to test the hypothesis that symptoms of anxiety and depression are associated with lower probability of subsequent live birth in women with infertility in the general population. The hypothesis was based on findings from earlier studies on women seeking help for their infertility (i.e. clinical studies) reporting associations between depressive [8, 9] or anxiety symptoms [10] and fertility outcomes [8, 10-14].

2. Method

2.1 Data sources and study sample

The present study is a cohort study in which the association of anxiety or depressive symptoms with probability of live birth in women with self-reported infertility was investigated. The study design is depicted in Figure 1. The cohort study was based on linked data from the North-Trøndelag Health Study 1995-1997 (HUNT 2) and the Medical Birth Registry of Norway (MBRN). HUNT 2 was a general health study aimed at the study of major public health issues in which all of the adult population of 127,000 in the county of North-Trøndelag in Norway was invited to participate [18]. Of the 94,194 individuals aged 19 years or older who were invited, 92,936 were eligible for participation. Out of these, 22 296 were women in the reproductive age span of 19-45 years, and out of these, 12 987 (58%) completed the study questionnaires. The flow chart in Figure 2 displays the procedure of sampling. ‘Questionnaire 1’ in HUNT 2 included the Hospital Anxiety and Depression Scale (HADS) and questions about demographic characteristics, somatic conditions, use of

medication, and life-style [19, 20]. ‘Questionnaire 2’ included questions about fertility-related problems, menstrual history, history of gynecological surgery, and use of contraceptives. The MBRN includes information about all pregnancies and births in Norway registered for antenatal care since 1967. In the present study, data from HUNT 2 was linked to a file including MBRN registrations until 2008.

Based on the information available, we identified a cohort of women with self-reported infertility at the time of HUNT 2 (Figure 2). Out of the 12 750 women in HUNT 2 who provided a valid answer to the question, ‘*Have you ever tried to get pregnant for more than one year?*’, 1772 (14%) answered ‘Yes’(Figure 2). However, some groups of women were excluded from the analysis file: Women who had live born children registered in the MBRN after the period of time in which they had unsuccessfully tried to get pregnant for more than 12 months (i.e. resolved infertility, $n=1\,089$) and women who were currently pregnant ($n=33$) were excluded as they were obviously not infertile anymore. Women who reported they had undergone either bilateral oophorectomy, total hysterectomy, or sterilisation ($n=39$) were excluded as they had no possibility of conceiving. Women who were using contraceptive pills or intrauterine devices (IUDs) ($n=51$) were excluded as they presumably had no intent of getting pregnant. After these groups were excluded, 497 women remained in the file. These women were regarded as infertile at HUNT 2 as they had tried for >12 months to get pregnant, they had no registrations of pregnancy or live birth in the MBRN after these 12 months and they did not use contraceptive pills or IUDs at HUNT 2. Further, four women were excluded as they had not completed the HADS-Anxiety (HADS-A) or HADS-Depression (HADS-D) sub-scales, and 26 were censored as their period of observation was <1 year, leaving $n=467$ women in the valid observed sample with current infertility at HUNT 2. The current project was approved by the Mid-Norway Regional Committee for Medical

Research Ethics (ref. no. 4.2007.275) and the Norwegian Data Inspectorate (ref.no. 08/01940-2/CGN). All women provided written informed consent to participate.

—Please insert Figures 1 and 2 here—

2.2 Anxiety and depressive symptoms

Symptom levels of anxiety and depression were measured by the Hospital Anxiety and Depression Scale (HADS) at HUNT 2 [19, 20]. HADS assesses depression and anxiety on two separate sub-scales, HADS-Anxiety (HADS-A) and HADS-Depression (HADS-D). Each sub-scale includes seven items. Each item is scored from 0-3 and six items are re-scaled before being summarised into sum scales with scores ranging from 0-21. Higher scores on the HADS-A or HADS-D sub-scales indicate higher levels of anxiety or depression symptoms. A score of ≥ 8 on the HADS-A or HADS-D sub-scale indicates symptom burden at case-level, i.e. probable anxiety or depressive disorder [20]. A score of ≥ 15 indicates symptomatology corresponding to severe anxiety or depression. HADS is reliable as a screening tool in the general population and has good psychometric properties in terms of factor structure, homogeneity, and internal consistency [20]. Internal consistencies of the HADS-A and HADS-D sub-scales were acceptable in the general population in HUNT 2 (Cronbach's α 0.80 and 0.76 for the HADS-A and HADS-D, respectively) [20] and in a clinical sample with infertility (Cronbach's α 0.87 and 0.75) [21]. HADS-A and HADS-D sub-scale scores at HUNT 2 were used as exposure variables in the present longitudinal study.

2.3 Follow-up time and outcome variable

Live birth was the primary outcome of the study. Survival time (years) was defined as time from participation in HUNT 2 to live birth registered in the MBRN, or until the end of

the period of observation 11 years after HUNT 2. In survival studies, participants for whom the outcome assessed is not an option, should be censored. Women were therefore censored from the valid observed sample as they turned 46 years. These women were no longer followed in the MBRN as they had reached an age in which getting pregnant is very unlikely.

2.4 Statistical analysis

Kaplan-Meier plots were employed to estimate the cumulative probability of live birth during the 11 years the women were followed in the MBRN. Kaplan-Meier plots were made for the sub-groups of women scoring above versus below the customary cut-offs of ≥ 8 for case-level anxiety or depression, as measured by the HADS sub-scales, respectively. Visual inspection of the plots was not suspicious for violation of the proportional hazards assumptions. The logrank test for equality of survivor functions was used to test for differences between the sub-groups with HADS-A ≥ 8 and/or HADS-D ≥ 8 , compared to the sub-groups below these cut-offs.

Cox proportional hazards regression analysis was used to estimate hazard ratios (HRs) for live birth and the corresponding 95% confidence intervals (CI) with time since HUNT 2 as the time scale, adjusting for the effect of potential confounders. Symptom levels as measured by the HADS-A and HADS-D sub-scales were used as exposure variables in these models. Variables that could confound the association between mental health and live birth in infertile women were entered as co-variables in the Cox proportional hazard model: age (years); completed level of education (≤ 9 , 10-12, 13-15, or ≥ 16 years); marital status (married/registered partner, unmarried, divorced/separated, or widow); hypothyroidism; Body Mass Index (BMI) (< 24.99 , ≥ 25.00); cigarette smoking (currently smoking daily or not); alcohol consumption (no alcohol consumption, 1-9 or ≥ 10 alcohol units (1 unit=1 glass of wine, beer or liquor) /week; duration of infertility and parity at HUNT 2. With the exception

of age (which was continuously scaled with no missing values), these co-variables were encoded as categorical, with missing data as separate categories. A posthoc power analysis was performed to assess the study's power to detect a difference of 25% of the live birth rate in the sub-group scoring ≤ 8 on both HADS sub-scales between the sub-group scoring ≥ 8 on one or both versus the sub-group scoring below the cut-offs on these sub-scales. This was done in a straight forward chi-square 2x2 table. All significance tests were two-tailed with an α -level of 0.05. Data analyses were performed using STATA 14.0 (StataCorp, College Station, Texas, US) in Windows 7 SP1.

3. Results

Descriptive statistics of the sub-samples according to exposure status (i.e. whether the women had case-level anxiety or depression defined as HADS-A ≥ 8 or HADS-D ≥ 8) is provided in Table 1. Ninety-four out of the 467 women in the observed sample scored HADS-A ≥ 8 , 36 scored HADS-D ≥ 8 , and altogether 104 women scored ≥ 8 on one or both HADS sub-scales. HADS-A and HADS-D were significantly correlated (Spearman's $\rho=0.58, p=0.000$).

—Please insert Table 1 here—

3.1 Survival analysis

In the survival analysis, the 467 women in the observed sample contributed 2,743 person-years (563 person-years from women with HADS-A ≥ 8 ($n=94$) and 217 with HADS-D ≥ 8 ($n=36$)). In average, the women in the sub-group with HADS-A ≥ 8 at HUNT 2 were followed in the MBRN for 5.99 years and the women in the sub-group with HADS-D ≥ 8 were followed for 6.03 years. After the women had been followed in the MBRN for 11 years, starting from the time of HUNT 2, their mean age had become 45 years (range 31-55). Two-

hundred-and-fifty-two women were ≥ 46 at the end of the follow-up period. Out of these, eight had given birth and were censored before they turned 46 years.

3.2 Incidence rates of live births

Overall incidence rate of live birth in the observed sample was 0.049 per year. Among the 467 women, 134 (28.7%) were registered with one or more live births during the period of observation. Among the 104 women with HADS-A ≥ 8 and/or HADS-D ≥ 8 , 34 (32.7%) were registered with live birth in MBRN during the period of observation (33.0% in the sub-group with HADS-A ≥ 8 and 30.6% in the sub-group with HADS-D ≥ 8). However, 100 (27.6%) of the 363 women with both HADS-A ≤ 7 and HADS-D ≤ 7 , i.e. below the cut-off for case-level symptomatology, were registered with live birth.

3.3 Survival times in women with case-level symptomatology

Survival estimates for the sub-groups with HADS-A ≥ 8 ($n=94$) or HADS-D ≥ 8 ($n=36$), respectively, as compared to sub-groups below the cut-offs, are shown in Figure 3 a) and b). The patterns of survival estimates appeared similar for anxiety (Figure 3 a)) and depression (Figure 3 b)). The logrank test with HADS-A ≥ 8 as exposure variable yielded an χ^2 of 0.05 ($p=0.478$), and in the test with HADS-D ≥ 8 as exposure variable, χ^2 was 0.01 ($p=0.935$). The incidence rates of live birth were 0.055 versus 0.047 in the sub-groups with HADS-A ≥ 8 versus HADS-A ≤ 7 , and 0.051 versus 0.049 in the sub-groups with HADS-D ≥ 8 versus HADS-D ≤ 7 .

Logrank test performed to test for differences in survival functions between the sub-group with HADS-A ≥ 8 and/or HADS-D ≥ 8 compared to the sub-group with HADS-A ≤ 7 and HADS-D ≤ 7 yielded an χ^2 of 0.48 ($p=0.488$). The study had 88 percent power to detect a 14 percent point difference in proportions of live births (i.e. 35 versus 21 percent women with

live birth in the follow-up period) between the sub-group scoring ≥ 8 on HADS-A and/or HADS-D sub-scales versus the sub-group scoring below the cut-off on both of these in a straight forward chi-square 2x2 table. Thus, the study was powered to detect even moderate differences in live birth rates between the sub-groups scoring above versus below the HADS-cut-offs for case-level anxiety or depressive symptomatology.

—Please insert Figure 3 here—

3.4 Cox proportional hazard models

In the unadjusted and adjusted Cox proportional hazard models, anxiety or depressive symptoms were not associated with live birth rates (Table 2). For the continuously scaled HADS-A, the crude HR for live birth was 1.004 (95% CI=0.96; 1.05) ($p=0.866$), and for HADS-D, HR was 0.98 (95% CI=0.92; 1.04) ($p=0.546$). The adjusted models were also non-significant (HR=0.99 (95%CI=0.94; 1.04) ($p=0.602$) for HADS-A and HR=1.01 (95% CI=0.94; 1.08) ($p=0.811$) for HADS-D). In the adjusted analyses, higher age, lower level of education, higher number of previous live born children, and longer duration of infertility were co-variables that were significantly associated with lower probability of live birth (all $p<0.05$) (Table 2).

4. Discussion

In the present prospective study of a sample of women with self-reported infertility from the general population, neither anxiety nor depressive symptoms at baseline were associated with lower rates of subsequent live births in women with self-reported infertility. In the 11-year study period, rates of live birth were comparable in the two sub-samples with and without case-level mental distress. These results therefore signify important arguments

against the hypothesis that anxiety or depressive symptoms contribute to the maintenance of female infertility. To our knowledge, this is the first population-based study investigating the prospective association between anxiety or depressive symptoms and live birth rates in infertile women. Still, there are two previous studies that may be mentioned as they investigated the prospective associations between mental health symptoms or conditions and incident infertility. A small case-control study of randomly selected women compared history of depressive symptoms between women with infertility and women who had given birth at a certain age [22]. In this study, women with a history of depressive symptoms were nearly twice as likely to report infertility than women without a history of depressive symptoms. However, a Finnish registry-study did not confirm a prospective association between anxiety or depression, and infertility [23]. The study compared rates of previous hospitalisations due to anxiety and depressive disorders in women who had had infertility treatment with rates of hospitalisations in age- and residence-matched controls from the general population. The study found similar odds ratios for hospitalisation due to anxiety and depressive disorders prior to infertility treatment in the women who had undergone infertility treatment as in population controls. These findings suggested that anxiety and depressive disorders do not predict infertility in the general female population. Notably, both of these studies used incident infertility as outcome, and thus their findings are not comparable to the present study, in which live birth in women who already were infertile was used as outcome.

The advantages of this study include the large, comprehensive study base, the longitudinal design with a long follow-up interval, and the fact that there was no attrition because outcomes were retrieved from the MBRN, which includes all live births in Norway. The investigation was fully blinded as to the hypothesis explored, and by employing a cohort study where participants were representative of the general population, we avoided the biases commonly seen in studies of women seeking help for infertility [17, 24, 25]. The associations

studied were adjusted for relevant confounders, and the study was sufficiently powered to detect significant differences in live birth rates between women exposed to symptom levels above versus below the HADS cut-offs for case-level symptomatology. However, since the study represents a zero finding, some limitations that may give rise to Type II error need to be noted. As in most population-based research, no 'gold-standard' diagnosis of infertility and its cause made by specialist was available. Fertility problems were self-reported, and there was no information about frequency and timing of sexual intercourse. This is, of course, a limitation of the study. The unintended inclusion of women without intentions of getting pregnant in the observed sample could represent a bias leading to lower incidence of live births and weaker associations, and inclusion of women who have not tried as much as 12 months to get pregnant may lower the reliability of findings. Further, some of the women may have changed partner after HUNT 2 and then given birth, or they may have had ART-treatment during the study period. Given an association between anxiety or depressive symptoms and live birth rates, not adjusting this association for the effect of ART-treatment may imply some residual confounding. However, a recent meta-analysis concluded that the association between distress and reduced pregnancy chances with ART is weak [13].

Consequently, the moderating effect of ART on the associations between anxiety, depression, and live birth in the present study is probably also weak. The lack of information as to the stability of symptoms of anxiety and depression during the 11-year follow-up period in the MBRN after HUNT 2 represents another limitation. However, we argue that the likelihood of a short episode of anxiety or depression to occur at the random time of the health study is low, whereas chronic cases are much more likely to be detected. This is probably the reason why anxiety and depression detected by HADS in randomly timed health studies seem to predict clinically relevant outcomes [26, 27]. Further, although a number of psychometric studies of the HADS observed a 2-factor solution with acceptable model fit for the HADS [21, 28], a

recent study evaluating the factor structure of the HADS in a sample of men and women at an infertility clinic concluded that a three-factor had better fit [21]. However, the above mentioned limitations, which may lead to increased risk of Type II error, may be partly outweighed by the larger statistical power due to the large sample size in the study. Further, the fact that the rates of live birth were similar in women with and without mental distress at case-level in the descriptive analyses suggest that the lack of association between anxiety or depressive symptoms and birth rates represents a 'true' zero finding, not a Type II error.

5. Conclusion

In this population-based cohort study, no evidence of a prospective association between anxiety or depressive symptoms, and live birth rates in women with self-reported infertility was found. These findings represent good news to women struggling with getting pregnant. The study signifies an argument against the hypothesis that anxiety and depressive symptoms are associated with lower probability of live birth in women with infertility. The study provides information which is useful for counselling couples who are worried that the woman's mental health issues could prolong their infertility. To our knowledge, this is the only existing population-based study investigating the prospective association of mental distress with birth rates in infertile women.

Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare that the authors have no competing interests to report.

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Ethics approval

The current project was approved by the Mid-Norway Regional Committee for Medical Research Ethics (ref. no. 4.2007.275) and the Norwegian Data Inspectorate (ref.no. 08/01940-2/CGN).

Data statement

Data are confidential and will not be shared.

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Table 1

Descriptive characteristics of valid observed sample according to exposure status (HADS- A and HADS-D sub-scales) (N=467).

	HADS-A ≥8 (n=94)	HADS-A ≤7 (n=373)	HADS-D ≥8 (n=36)	HADS-D ≤7 (n=431)	Total (N=467)
	<i>M (SD)</i>	<i>M (SD)</i>	<i>M (SD)</i>	<i>M (SD)</i>	<i>M (SD)</i>
	range	range	range	range	range
Age (years)	33 (6.8)	35 (6.1)	34 (7.0)	35 (6.2)	34 (6.2)
	22-44	20-44	20-43	21-44	20-44
Duration of infertility (years)	8.7 (6.20)	8.5 (6.34) 0-24	8.3 (6.24) 0-22	8.6 (6.31) 0-24	8.6 (6.31) 0-24
	0-23				0-24
HADS anxiety sub-scale	10.3 (2.30)	3.2 (2.05)	10.0 (3.71)	4.2 (3.13)	4.7 (3.13)
	8-17	0-7	3-17	0-14	0-17
HADS depression sub-scale	5.6 (3.24)	2.0 (2.07)	9.7 (1.80)	2.1 (1.89)	2.7 (2.07)
	0-15	0-15	8-15	0-7	0-15
	<i>n (%)</i>	<i>n (%)</i>	<i>n (%)</i>	<i>n (%)</i>	<i>n (%)</i>
Type of infertility					
Primary	63 (67)	213 (57)	23 (64)	253 (59)	276 (59)
Secondary	31 (33)	160 (43)	13 (36)	178 (41)	191 (41)
Number of liveborn children at HUNT 2 ^a					
0	63 (67)	213 (57)	23 (64)	253 (59)	276 (59)
1	25 (27)	116 (31)	9 (25)	132 (31)	141 (31)
2	5 (5)	36 (10)	4 (11)	37 (9)	41 (9)
3	1 (1.1)	5 (1.3)	0 (0)	6 (1.4)	6 (1.3)
4-9	0 (0)	3 (0.8)	0 (0)	3 (0.7)	3 (0.6)
Number of live births during the period of observation (11 years) ^a					
0	63 (67)	271 (73)	25 (69)	309 (72)	334 (72)
1	13 (14)	41 (11)	6 (17)	48 (11)	54 (12)
2					

3	11 (12)	40 (11)	2 (6)	49 (11)	51 (11)
4	7 (8)	20 (5)	3 (8)	24 (6)	27 (6)
	0 (0)	1 (0.3)	0 (0)	1 (0.2)	1 (0.2)
Has seen a doctor due to problems with getting pregnant	70 (75)	279 (75)	27 (75)	322 (75)	349 (75)
Education					
≤9 years	17 (18)	53 (14)	5 (14)	65 (15)	70 (15)
10-12 years	57 (6)	216 (58)	23 (63)	250 (58)	273 (58)
13-15 years	13 (14)	62 (17)	7 (19)	68 (16)	75 (16)
≥16 years	6 (6)	39 (11)	1 (2.7)	44 (10)	45 (10)
Marital status					
Married/registered partner	47 (50)	199 (53)	17 (50)	229 (53)	246 (53)
Unmarried	38 (49)	125 (34)	16 (44)	147 (34)	163 (34)
Divorced/separated	7 (8)	42 (11)	3 (8)	46 (11)	49 (11)
Widow	2 (2.1)	4 (1.1)	0 (0)	6 (1.4)	6 (1.3)
Hypothyroidism	7 (8)	10 (2.7)	1 (2.7)	16 (4)	17 (4)
Body Mass Index					
≤18.49	0 (0)	4 (1.1)	0 (0)	4 (0.9)	4 (0.9)
18.50-24.99	52 (55)	190 (51)	15 (42)	227 (53)	242 (53)
25.00-29.99	28 (30)	116 (31)	11 (31)	133 (31)	144 (31)
≥30.00	14 (15)	63 (17)	10 (28)	67 (16)	77 (17)
Daily cigarette smoking	50 (53)	161 (43)	22 (61)	189 (44)	211 (44)
Use of alcohol (units per week)					
None	22 (23)	90 (24)	9 (25)	103 (24)	112 (24)
1-9	57 (61)	235 (63)	22 (61)	270 (63)	292 (63)
≥10	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Note: Missing values are not reported and therefore percentages do not always add up to 100.

Two-hundred-and-forty-four women were censored as they turned 46 years (i.e. were no longer regarded as fertile-aged) during the period of observation.

^aInformation from the Medical Birth Registry of Norway (MBRN).

M, mean; *SD*, standard deviation.

Table 2

Cox proportional hazard models with HADS- A and HADS-D sub-scales as exposure variables and live birth as 'event' (N=467).

Model	Anxiety			Depression		
	HR	95% CI for HR	<i>p</i>	HR	95% CI for HR	<i>p</i>
Crude	1.004	0.96; 1.05	0.866	0.98	0.92; 1.04	0.546
Adjusted						
Age (years)	0.90	0.85; 0.94	0.000	0.90	0.85; 0.94	0.000
Education ^{a,b} (years)						
13-15	0.72	0.38; 1.35	0.301	0.71	0.38; 1.35	0.296
10-12	0.52	0.29; 0.95	0.034	0.51	0.28; 0.94	0.032
≤9	0.54	0.23; 1.27	0.159	0.53	0.23; 1.24	0.143
missing	0.19	0.02; 1.48	0.113	0.19	0.02; 1.46	0.110
Marital status ^{a,c}						
Unmarried	0.97	0.65; 1.46	0.901	0.96	0.64; 1.45	0.850
Divorced/separated	0.73	0.29; 1.86	0.514	0.73	0.29; 1.85	0.504
Widow	0.00	0; .	1.000	0.00	0; .	1.000
missing	2.00	0.27; 15.10	0.501	2.00	0.27; 15.16	0.499
Hypothyreosis	1.18	0.45; 3.09	0.730	1.17	0.45; 3.03	0.753
BMI≥25.00	0.98	0.84; 1.13	0.740	0.97	0.83; 1.13	0.680
Daily cigarette smoking	0.76	0.51; 1.12	0.170	0.75	0.51; 1.11	0.152
Alcohol use ^{a,d} (units/week)						
1-9	1.01	0.67; 1.51	0.980	1.01	0.67; 1.52	0.976
≥10	-	-	-	-	-	-
missing	0.61	0.32; 1.17	0.140	0.61	0.32; 1.16	0.130
Parity	0.61	0.43; 0.87	0.005	0.61	0.43; 0.87	0.006
Duration of infertility	0.89	0.84; 0.95	0.000	0.89	0.84; 0.95	0.000
Fully adjusted	0.99	0.94; 1.04	0.602	1.01	0.94; 1.08	0.811

^aVariables were entered as 'dummy' variables, ^bReference category, ≥ 16 years education, ^cReference category, married/registered partner,

^dReference category, never uses alcohol

HR, Hazard ratio; CI, confidence interval; BMI, body mass index

HIGHLIGHTS

- Mental distress is not associated with probability of live birth in infertile women
- Live birth rates are similar in infertile women with and without anxiety
- Live birth rates are similar in infertile women with and without depression
- Time to live birth are comparable in all sub-groups